## REMARKS/ARGUMENTS

Prior to the present amendment, claims 1-88 were pending in this application. Claims 1-22, 29-39, 53-63, and 74-88 were withdrawn from consideration, and claims 23-28, 40-52 and 64-73 were rejected on various grounds. The present amendment includes cancellation of non-elected claims 1-22, 29-39, 53-63, and 74-88, and the amendment of claims 23, 24, 43, 44, 46, 47, 67, 68, 70, 71, and 72. All cancellations and amendments were made without prejudice or disclaimer. Applicants specifically reserve the right to pursue any deleted subject matter in one or more continuing applications. The amendments are fully supported by the specification as originally filed, and do not add new matter. Specific support for the amendment of claims 23, 47 and 71 is at least in Example 5 and Figure 4.

### *Election/Restrictions*

Applicants note the finality of the restriction requirement.

### *Claim Rejections - 35 U.S.C. § 112*

Claims 23-28, 40-52, and 64-73 were rejected under 35 U.S.C. 112, second paragraph, as allegedly "indefinite for failing to particularly point out and distinctly claims the subject matter which applicant regards as the invention." In particular, claims 23, 47 and 71 were held "indefinite" in their recitation of "detecting phosphorylation." According to the rejection, the scope of this phrase is indefinite, since it is unclear if the detection of the degree of phosphorylation is meant. The claims have now been amended to recite that the level of phosphorylation is determined, which is believed to obviate this rejection.

### *Claim Rejections – 35 U.S.C. § 102*

(a) Claims 23-28, 40, 42, 46-52, 64, 66, and 70 have been rejected under 35 U.S.C. 102(b) as allegedly being anticipated by Thor *et al.* (J. Clin. Oncol. 18(18):3230-3239 (2000)). According to the rejection, "Thor teaches the claimed methods because Thor's methods comprise the same active steps as recited in the claims." While the Examiner acknowledges that Thor's method does not have the same intended use as the intended use set forth in the rejected claims, the claims are rejected since "the active steps in Thor are the same as in the claims and the

intended use recited in the claims does not appear to materially affect the active steps of the claimed methods."

Upon entry of the current claim amendments, it should be clear that the claimed methods include the affirmative step of identifying the tested HER2-positive tumor cells as responsive to treatment with an antibody inhibiting the association of HER2 with another member of the ErbB receptor family, if a significant level of phosphorylation is determined (step (c) of claim 23), or predicting that a subject diagnosed with a HER2-positive tumor is likely to respond to treatment with an antibody inhibiting the association of HER2 with another member of the ErbB receptor family, if the level of phosphorylation of an ErbB receptor in a biological sample obtained from the subject is at a significant level (step (c) of claim 47). These amendments present the rejected claims in a format similar to the format of claim 71, and its dependent claims (claims 72 and 73), which were not rejected under this section. Accordingly, the Examiner is respectfully requested to reconsider and withdraw the present rejection.

(b) Claims 23-28, 40, 42-44, 47-52, 64, and 66-68 were rejected under 35 U.S.C. 102(b) as allegedly being anticipated by Wildenhain *et al.* (Oncogene, 5(6):879-883 (1990)). Just as in the previous rejection, the examiner acknowledges that "Wildenhain's method does not appear to have the same intended use as the intended use set forth in the claims." However, the claims are rejected, since "Wildenhain's methods comprise the same active steps as recited in the claims."

Upon entry of the current claim amendments, it should be clear that the claimed methods include the affirmative step of identifying the tested HER2-positive tumor cells as responsive to treatment with an antibody inhibiting the association of HER2 with another member of the ErbB receptor family, if a significant level of phosphorylation is determined (step (c) of claim 23), or predicting that a subject diagnosed with a HER2-positive tumor is likely to respond to treatment with an antibody inhibiting the association of HER2 with another member of the ErbB receptor family, if the level of phosphorylation of an ErbB receptor in a biological sample obtained from the subject is at a significant level (step (c) of claim 47). These amendments present the rejected claims in a format similar to the format of claim 71, and its dependent claims (claims 72 and 73), which were not rejected under this section. Accordingly, the Examiner is respectfully requested to reconsider and withdraw the present rejection.

(3) Claims 23-28, and 42-44 were rejected under 35 U.S.C. 102(b) as allegedly being anticipated by Xu *et al.* (Int. J. Cancer, 59:242-247 (1994)). According to the rejection, Wu et al. teaches the same active steps as recited in the claims, although does not have the same intended use as the intended use set forth in the rejected claims.

Since the claims now recite the affirmative step of identifying the tested HER2-positive tumor cells as responsive to treatment with an antibody inhibiting the association of HER2 with another member of the ErbB receptor family, if a significant level of phosphorylation is determined (step (c) of claim 23), which is not included in Xu et al., the present rejection should be withdrawn.

(4) Claims 23-28, and 42-44 were rejected under 35 U.S.C. 102(b) as allegedly being anticipated by Ignatoski *et al.* (Endocrinology, 140:3615-3622 (1999)). According to the rejection, Ignatoski et al. teaches the same active steps as recited in the claims, although does not have the same intended use as the intended use set forth in the rejected claims.

Since the claims now recite the affirmative step of identifying the tested HER2-positive tumor cells as responsive to treatment with an antibody inhibiting the association of HER2 with another member of the ErbB receptor family, if a significant level of phosphorylation is determined (step (c) of claim 23), which is not included in Ignatoski et al., the present rejection should be withdrawn.

***Claim Rejections – 35 U.S.C. § 103***

(1) Claims 23, 41, 47, 65 and 71-73 were rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over DiGiovanna *et al.* (Cancer Res. 55:1946-1055 (1995)) in view of Terstappen (US 6,365,362, issued April 2, 2002).

DiGiovanna et al. was cited for its alleged teaching of using immunohistochemistry on formalin-fixed and paraffin-embedded surgical specimens from human breast tumors, using the PN2A antibody, which is specific for phosphorylated HER2. DiGiovanna et al. was further relied on for allegedly teaching that the extent of p185 (Her2) tyrosine phosphorylation varies considerably, and that it is highly likely that measurement of p185(Her2) signaling activity as opposed to p185 abundance will greatly enhance methods that use detection of p185 for prognosis and treatment decisions, and that tumors most vulnerable to anti-p185 antibodies will

be those that are dependent upon p185 signaling for growth. The Examiner acknowledges that DiGiovanna fails to teach the method using samples of circulating tumor cells.

Terstappen is cited for its alleged teaching that carcinoma cells in the blood may be assayed immunocytochemically to characterize circulating tumor cells.

According to the rejection, "it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have modified DiGiovanna's method so that it could be used in the measurement of Her2 phosphorylation status of circulating tumor cells." The Examiner finds motivation for combining the two references, "because collecting a blood sample to analyze the Her-2 status of circulating cancer cells is less invasive than collecting a tissue sample from the cancer."

The rejection is respectfully traversed.

Claims 23 and 41 are directed to the identification of tumor cells responsive to treatment with an antibody inhibiting the association of HER2 with another member of the ErbB receptor family, following a three-step method, which includes determination of the level of phosphorylation of an ErbB receptor in a biological sample (claim 23), and specifically in a biological fluid comprising circulating tumor cells and/or circulating plasma proteins (claim 41). The claims further include the step of identifying the HER2-positive tumor cells as responsive to treatment with such antibody, if a significant level of phosphorylation is determined.

Claims 47 and 65 are drawn to a method of predicting the response of a subject diagnosed with a HER2-positive tumor to treatment with an antibody inhibiting the association of HER2 with another member of the ErbB receptor family, following a three-step method, which includes the determination of the level of phosphorylation of an ErbB receptor in a biological sample obtained from the subject (claim 47), and specifically, in a biological fluid comprising circulating tumor cells and/or circulating plasma proteins (claim 65), and predicting that the subject is likely to respond to treatment with such antibody, if a significant level of phosphorylation is determined.

Claims 71-73 are directed to a three-step method of identifying a subject responsive to treatment with an anti-HER2 antibody, including determining the level of phosphorylation of an ErbB receptor in circulating tumor cells of the subject, and determining that the subject is likely to respond to treatment with an anti-HER2 antibody, if a significant level of phosphorylation is detected.

DiGiovanna *et al.* report that the extent of tyrosine phosphorylation of p185 (HER2) varied considerably in paraffin-embedded sections of five p185-overexpressing breast tumors, using an antibody that specifically recognizes the tyrosine phosphorylated form of p185. In particular, DiGiovanna *et al.* merely demonstrated that out of five p185-overexpressing breast tumors, only two showed reactivity with their antibody, i.e. appeared to be tyrosine phosphorylated, while the other p185-overexpressing breast tumors did not react with the antibody, i.e. did not appear to be tyrosine phosphorylated. Based on these extremely limited data, considering tyrosine phosphorylation as a surrogate for p185 signaling activity, the authors tentatively suggest that "the tumors most vulnerable [to treatment with anti-p185 monoclonal antibodies] might be those which are dependent upon p185 signaling for growth," and "[i]f so," their antibody "may be uniquely suitable for predicting responses to anti-p185 immunotherapy." (Emphasis added.) There is no experimental evidence for these tentative suggestions, other than the finding that the extent of tyrosine phosphorylation of p185 varies in a subset of a very small sample (five!) of p185-overexpressing breast tumors. The authors state: "Similar data have been obtained on a much larger sample of frozen sections of mammary carcinomas analyzed using our original polyclonal antibody," (page 1954, first column), citing Padhy *et al.*, Cell 28(4):865-71 (1982). However, the Padhy *et al.* paper (Abstract enclosed) merely reports the identification of a phosphoprotein induced by the transforming DNA of rat neuroblastomas, using polyclonal antisera, and is therefore a reference for the availability of the polyclonal antibody. The data claimed to be obtained "on a much larger sample of frozen sections of mammary carcinomas," are not reported.

One of ordinary skill would recognize that experiments conducted on a panel of five tumor samples do not produce any meaningful, statistically significant data, and are not suitable for drawing any meaningful, scientifically acceptable conclusions. Thus, the results of DiGiovanna do not even establish in a credible way that in some HER2-overexpressing breast tumors HER2 is tyrosine phosphorylated while in others it is not, and certainly form no basis for the suggestion that out of HER2-overexpressing breast tumors the ones in which HER2 is tyrosine phosphorylated would be expected to respond better to treatment with anti-HER2 antibodies than those in which HER2 is not tyrosine phosphorylated.

Furthermore, the claims pending in this application address the responsiveness of HER2-positive tumor to antibody treatment, and are not limited to HER2-overexpressing tumors. The

phrase "HER2-positive" is another way of referring to e HER2- (ErbB2)-expressing cancer, which, in paragraph [0096] is defined, as "one comprising cells which have ErbB protein present at their cell surface," and which "produces sufficient levels of ErbB2 at the surface of cells thereof, such tat an anti-ErbB2 antibody can be thereto and have a therapeutic effect with respect to the cancer." DiGiovanna *et al.* provide no information, whatsoever, about HER2-positive cancer in general. Based on the data and general teaching of DiGiovanna *et al.* one would not be able to determine if HER2-positive tumors in general have subgroups, characterized by the presence and absence of HER2 phosphorylation, respectively, and whether such differences, if present, would have any biological significance.

Finally, claims 23, 41, 47, and 65 address the responsiveness of HER-positive tumors to treatment with antibodies inhibiting the association of HER2 with another member of the ErbB receptor family, and not HER2 antibodies in general. DiGiovanna *et al.* have no disclosure, teaching or suggestion concerning the prediction of patient response to this specific class of antibodies.

The secondary reference, Terstappen was cited for its teaching that carcinoma cells in the blood may be assayed immunocytochemically to characterize circulating tumor cells, and does not remedy the deficiencies of the primary reference.

Accordingly, the combination of DiGiovanna *et al.* and Terstappen does not make obvious the invention claimed in the rejected claims, and the Examiner is respectfully requested to reconsider and withdraw the present rejection.

(2) Claims 23, 43, 45, 47, 67 and 69 were rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over DiGiovanna *et al., supra.*

According to the rejection, DiGiovanna demonstrates an immunoblot technique, where a phosphor-ErbB receptor band on a gel is detected and separately an immunohistochemistry technique using a phospho-specific anti-ErbB2 receptor antibody. In addition, DiGiovanna is stated to teach that the prior art teaches methods of quantification of tyrosine receptor phosphorylation in tumor samples by immunoprecipitation of receptors and then immunoblottting with an anti-phorphotyrosine antibody, and that such experiments are subject to inaccurate interpretations because of variability in tissue content of stroma/normal cells versus tumor cells and because of tumor cell heterogeneity. From this, the Examiner concludes that "it

would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used DiGiovanna's immunohistochemical method to confirm earlier results obtained by immunoprecipitation followed by immunoblotting.

This rejection appears to be based on the assumption that the rejected claims rely on certain specific methods used to identify ErbB receptor phosphorylation for patentability. This is not the case. As explained in response to the previous rejection under 35 USC 103 above, the claimed inventions are non-obvious over DiGiovanna *et al.* since this reference has no credible disclosure, teaching or suggestion concerning the prediction of patient response to ErbB antibodies, especially the specific class of antibodies specified in independent claims 23 and 47. Accordingly, the present rejection is believed to be misplaced, and its withdrawal is respectfully requested.

All claims pending in this application are believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited.

Please charge the fees for extension of time, and any additional fees that may be required, or credit overpayment to Deposit Account No. **08-1641**, referencing Attorney's Docket No. **39766-0114A**.

Respectfully submitted,

Date: December 21, 2006

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1: Cell. 1982 Apr;28(4):865-71.



**Identification of a phosphoprotein specifically induced by the transforming DNA of rat neuroblastomas.**

**Padhy LC, Shih C, Cowing D, Finkelstein R, Weinberg RA.**

DNAs from nitrosoethylurea-induced rat neuroblastomas transform NIH/3T3 mouse fibroblasts in a transfection assay. DNAs of such transformed cells can be used in a subsequent cycle of transfection to generate secondary foci that contain virtually no foreign genetic material besides the sequences carrying the rat neuroblastoma transforming function. These secondary neuroblastoma transfectants were injected into young mice and grew out into fibrosarcomas. Sera from these mice were examined for reactivity with any proteins which were induced specifically by the neuroblastoma transforming sequence. These sera precipitate a polypeptide of about 185,000 daltons from 35S-methionine-labeled cell lysates of the rat neuroblastoma cells that served as DNA donors and in all transfection-derived primary and secondary foci. This protein is present in high levels in all neuroblastoma transfectant clones, but was not detectable in a variety of other transformed cells. Antisera were prepared from mice bearing tumors induced by transformed cells derived by transfection of DNAs from various tumor cell types unrelated to rat neuroblastoma. These antisera failed to immunoprecipitate the 185,000 dalton protein. These data indicate that the synthesis of the 185,000 dalton protein is specifically induced by the neuroblastoma transforming sequence. The protein may be encoded by the transforming sequence and may mediate transformation in this chemically induced tumor.

PMID: 7094016 [PubMed - indexed for MEDLINE]